Synopsis for Ph.D. Dissertation

Formulation and Evaluation of Microneedle Drug Delivery System for Diabetes Management

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1. Introduction

The stratum corneum, the outermost layer of the skin consists of densely packed corneocytes surrounded by a rigid, impermeable protein-lipid envelope, all embedded within an intercellular lipid matrix. It acts as an effective primary barrier preventing the penetration of contaminants and topically applied agents (1). This layer with a thickness of 10-20 µm (2,3), serves as the primary biological barrier to drug delivery, limiting the efficacy of transdermal drug delivery systems (4). Additionally, it prevents transepidermal water loss from the body and restricts active pharmaceutical and cosmetic ingredients from reaching the epidermis or dermis (5–7). The second barrier composed of tight proteins junction, which are most concentrated in the stratum granulosum layer of the epidermis (8). Moreover, adequate skin hydration is essential for maintaining healthy skin (9), as studies suggest that hydration levels significantly influence skin permeability (10). To overcome the epidermal barrier, various physical penetration enhancement methods are used which includes electroporation, sonophoresis, and iontophoresis, microneedles (MNs) (11).

The concept of microneedles for drug delivery was first reported in 1971 by Martin S Gerstel and Virgil A Place (12). Microneedles are arrays of micrometer-sized solid needle-like projections. There are various types of MNs such as solid, coated, hollow, dissolving microneedles (DMNs) and hydrogel-forming microneedles. Solid, coated and hollow MNs are constructed from materials like silicon, metal, and glass. In contrast, dissolving microneedles are generally made from carbohydrates such as chitosan, sucrose, dextran and mannitol as well as biocompatible polymers. Biodegradable and water-soluble polymers commonly used in DMNs include hyaluronic acid (13,14), pullulan (15), sodium alginate (SA), guar gum (GG), xanthan gum (XG) (16), polyvinylpyrrolidone (PVP) (17), and polyvinyl alcohol (PVA) (18). Non-degradable materials like polydimethylsiloxane (PDMS), polyvinyl methyl ether (PMVE) and polyacrylic acid (PAA), (19) are also employed in certain applications. Biodegradable polymers play a crucial role in dissolving microneedles formulation due to their broad range of applications (20). This technology allows drugs and other pharmaceutical bio-actives to be encapsulated within

MNs composed of biocompatible and water-soluble materials (21,22). Targeted drug delivery occurs when the needle tips of drug-loaded dissolving microneedles dissolve rapidly upon contact with skin fluids in deeper skin layers, releasing the drug payload (23-25). To date, microneedles technology has been developed to enable painless transdermal delivery of therapeutic agents, providing a user-friendly alternative to traditional invasive injections (26).

Types of Microneedles:-

Microneedles have been developed in various forms, including solid, hollow, coated and hydrogel, dissolving types, each designed for specific drug delivery applications. These microneedles employ distinct mechanisms to facilitate drug penetration into the epidermis.

Solid Microneedles:-

Solid microneedles are usually made of silicon, ceramic, metal and glass, non-biodegradable polymer. The release of drug from the solid MNs is carried out by "poke and patch". Solid MNs are primarily used to pre-treat the skin by creating microscopic pores. When a drug patch is applied over the area having micro channels the absorption of drug is enhanced. This process improves permeation rates, allowing the drug to enter the skin and be absorbed by capillaries, leading to either localized or systemic effects. Drug delivery through solid microneedles relies on passive diffusion, utilizing durable materials to achieve controlled administration (27).

Coated Microneedles:-

The coated MNs are similar to solid MNs except that they are coated with solution or dispersion of drug. The drug release of coated MNs follows the principles of "coating and poking". The drug solution or dispersion layer is uniformly coated onto the microneedles (MNs). Upon insertion into the skin, the drug rapidly dissolves and is released, after which the MNs are removed. The maximum drug-loading capacity depends on the needle size typically very small and the thickness of the coating layer (28).

Hollow Microneedles:-

The drug release approach of hollow microneedles (MNs) is mainly through "poke and flow". There is an internal cavity filled with a drug solution or dispersion. These microneedles are perforated at the tips, allowing the drug to be directly delivered into the epidermis upon insertion. They are primarily used for delivering high molecular weight (MW) compounds such as oligonucleotides, proteins and vaccines. The hollow structure enables the injection of larger drug doses. However, maintaining an optimal discharge rate is crucial. While larger needle

openings enhance flow rates, they compromise durability and precision. To improve sharpness and structural integrity, metal coatings can be applied (29).

Dissolving Microneedles:-

Dissolving microneedles (DMNs) consists of biodegradable polymers that incorporate the drug within their matrix. Upon insertion into the skin, these microneedles dissolve, releasing the drug without requiring removal. The degradation of the polymer within the epidermis regulates drug release. The polymer's bioacceptability and solubility in the skin make it ideal for long-term use. This approach enhances patient compliance (30).

Hydrogel-Forming Microneedles:-

Hydrogel-forming microneedles (MNs) consist of a swelling polymer matrix and a drug reservoir. Upon insertion, they absorb interstitial fluid (ISF), causing the microneedles to swell and facilitating drug diffusion. These microneedles are typically made from synthetic polymers and can effectively deliver both macromolecules and micromolecules. This technology offers promising applications in subcutaneous drug delivery, particularly in glycemic control and chronic disease management. Its pain-free drug administration approach enhances patient comfort and compliance (31).

Dimensions of Microneedles

Microneedles are specifically designed to avoid stimulating sensory receptors in the skin’s upper layer. Ideally, they should have a maximum length of 150-1500 µm, a width of up to 50-250 µm, and a tip diameter should be up to 1-25µm (32,33). The goal is to create a painless delivery system.

Microneedles Fabrication Material and Their Properties

A number of techniques such as micromoulding, air blowing, lithography, etc are employed to fabricate microneedles. Table 1 compares different techniques employed in microneedle fabrication giving their advantages and limitations (34).

Table 1: Methods of fabrication

Method	Description	Advantages	Limitations
Micromoulding	Microneedle arrays are cast from polydimethylsiloxane (PDMS), moulds that act as master template	-Simple fabrication process -Cost-efficiency -Easily scalable	-Time intensive process -Not suitable for thermolabile drugs
Droplet-born Air Blowing	Polymer droplets using air-blowing technique to form 3D microneedles	-Moderate preparation condition -Drug loading process is easy	-Complex shapes are difficult to producing
Drawing Lithography	Thermal, magnetorheological, or ultraviolet (UV) methods to form microneedles (MNs)	-Extremely high aspect ratios for fabrication of microneedles	-Not applicable for heat or light sensitive drugs
Electro-drawing	Microneedles are formed by using electrical discharges	-Suitable for producing complex microneedles without deformation	-Preparation method is difficult -Manufacturing cost is high
Photolithography	A technique involving patterned thin films embedded with active agents to fabricate microneedles	-Economical for production -Producing of fine, small-scale features	-High cost for new technology -Complex process
Continuous Liquid Interface Production	A continuous (non-layered) technique used for microneedle fabrication	-Simple and rapid process -Capable of producing a different types of microneedle shapes	-Not compatible for sensitive drug compounds

Microneedles have been fabricated using different materials, which are described as follows:-

Silicon:-

In the 1990s, silicon was the first material used in the fabrication of microneedles (MNs). As a crystalline material with an anisotropic structure, silicon offers flexibility, allowing for the

fabrication of needles in various sizes and configurations (35). Its desirable physical properties make it a versatile material, and silicon substrates can be precisely manufactured in large quantities. However, its application in microneedles is limited due to high costs, a complex and time-consuming fabrication process, and concerns regarding biocompatibility (36).

Metals:-

Stainless steel and titanium are among the most commonly used metals for fabrication of microneedles, owing to their excellent mechanical strength and biocompatibility. Compared to metals or silicon are more durable and resistant to fracturing, making them a preferred choice. Stainless steel was the first metal used in microneedle fabrication, while titanium serves as a strong alternative due to its favorable properties (37).

Ceramic Alumina (Al_2O_3):-

Ceramic alumina (Al_2O_3) is primarily used for its superior chemical resistance. More recently, Ormocer®, an organically modified ceramic, has gained attention in microneedle fabrication (38). This copolymer features three-dimensional cross-links, and its properties can be tailored by incorporating different organic units during polymerization. Typically, ceramic microneedles are produced using micromoulding techniques (39).

Carbohydrates:-

Maltose is the most widely used carbohydrate in production of microneedles, though other carbohydrates such as xylitol, trehalose, galactose, sucrose, mannitol and polysaccharides are also employed. These microneedles are formed by casting drug-loaded carbohydrate mixtures into molds created from metal or silicon templates. Drug release into the epidermis occurs through the time-dependent dissolution of the carbohydrate structure (40).

Polymers:-

A wide variety of polymers have been utilized in microneedle fabrication, including poly(lactic-co-glycolic acid), poly lactic acid, poly(methyl methacrylate), cyclic olefin copolymer, polycarbonate, poly(vinyl pyrrolidone), poly glycolic acid, polystyrene (PS), , poly(methyl vinyl ether-co-maleic anhydride), poly(vinyl alcohol). Most microneedle arrays derived from these polymers are designed to be dissolving, hydrogel-forming or biodegradable for drug delivery applications (41).

Microneedles have certain advantages which make them preferable over other topical dosage forms for topical delivery of drugs Table 2 (42).

Table 2: Comparative analysis of microneedles and other topical dosage forms used for drug delivery systems

Aspect	Topical Cream	Transdermal Patch	Hypodermic Needle	Microneedle
Formulation types	Lotion, gel, or cream	Adhering medicated patch to the skin	Thin, hollow tube with a pointed end for injection	Micron-sized needles are arranged on a patch
Speed of effect	Gradual onset	Gradual effect	Rapid response	Quick absorption
Self-application	Can be applied by the self	Self-use	Requires professional administration	Can be self-applied
Drug absorption efficiency	Low absorption	Limited absorption	High absorption	High absorption
Ease for patients	Lower comfort and adherence	More user-friendly	Discomfort	Higher comfort
Pain	Painless	Painless	Causes pain	Painless
Mechanism of drug penetration	Penetrates through surface skin openings	Penetration across stratum corneum barrier	Injected straight into underlying skin layers	By passes stratum corneum barrier; reaches deeper skin layers

2. Review of Literature

Diabetes mellitus is a chronic metabolic disorder caused by insufficient insulin secretion or ineffective insulin utilization, leading to persistently high blood glucose levels (hyperglycemia). This condition arises due to inadequate insulin production by the pancreas or the body's inability to regulate glucose properly (43). Diabetes mellitus is currently recognized as one of the most widespread epidemics globally, with its incidence steadily increasing. In 2015, it was estimated that 415 million people had diabetes, and recent projections suggest that by 2040, more than 642

million individuals will be affected (15). In 1997, the American Diabetes Association (ADA) classified diabetes mellitus into three main types (44):

1. **Type 1 Diabetes (Juvenile Diabetes or Insulin-Dependent Diabetes Mellitus)**- Caused by the destruction of beta cells in the islets of Langerhans within the pancreas, leading to minimal or no insulin production.
2. **Type 2 Diabetes (Adult-Onset Diabetes or Non-Insulin-Dependent Diabetes Mellitus)**- Characterized by insulin resistance, a condition in which the body's cells do not respond effectively to insulin.
3. **Gestational Diabetes**- Develops during pregnancy and usually resolves after childbirth.

Insulin therapy is currently the most effective approach for achieving normoglycemia in diabetes and minimizing associated complications. Due to its impaired oral bioavailability, insulin is usually administered via subcutaneous (SC) injection. However, SC administration is associated with several limitations, including local inflammation, reduced patient compliance and risk of infection. Repeated injections at the same site can also lead to skin thickening and low glycemic control, ultimately resulting in suboptimal diabetes management. To overcome these drawbacks, researchers have investigated non-invasive delivery routes, such as oral, pulmonary, peritoneal, buccal, nasal, and transdermal methods. Among these, transdermal delivery of insulin has gained significant attention in recent decades, owing to its easy self-administration and potential to enhance patient adherence. More recently, the use of microneedles (MNs) has emerged as a promising strategy. MNs provide rapid insulin absorption due to the high density of capillaries in the stratum papillare of the skin. The first study concerning the use of MNs for insulin delivery was reported in 2003 (15).

Table 3 summarizes research work carried out using different antidiabeties formulated into microneedles employing various polymers for the management of diabetes, highlighting their key findings.

Table 3: Studies on management of diabetes using microneedles based drug delivery systems

Polymers	Drug	Fabrication method/types	Outcomes
Pullulan	Insulin	Micromoulding/ dissolving microneedle	-Good thermal stability, (Td_{max}=294°C). -Strong mechanical properties, (>0.15 N/needle). -Penetrating depth of 381 μm, *in vitro* skin tests. -Dissolves within 2 h *in vitro*, releasing up to 87% of the encapsulated insulin. -Maintains non-cytotoxicity after 4 weeks of storage at 4, 20 and 40°C (15).
Pullulan	Fluorescein isothiocyanate/ bovine serum albumin and insulin	Micromoulding/ dissolving microneedle	-MNs are transdermal delivery of both low and high molecular weight of drug molecules. -Mechanically strong, biocompatible, and self dissolving (45).
Sodium hyaluronate	Exenatide	Micromoulding/ dissolving microneedle	-Sufficient mechanical strength. -Fast dissolve and release the drug within 2 min. -Easily penetrate the skin *in vitro* and *in vivo*. -Transepidermal water loss tests recovered skin barriers within 10-12 h after MN application. -Pharmacological active and one month storage (46).
Calcium alginate/sodium alginate	Exenatide	Micromoulding	-Adequate mechanical strength. -Matrix layer dissolves and tip layer show sustained drug release.

			-High activity, storage at room temperature for long-term. -*In vitro* release for 48 h, high relative bioavailability 83.04%. -A single dose delivers a low blood glucose lasting ~24 h, maintaining efficacy with repeated administration without inducing drug resistance (47).
Poly (lactic-co-glycolic acid) nanoparticles/polyvinylpyrrolidone /polyvinyl alcohol	Liraglutide	Dissolving microneedle	-Derma-roller was used as the master mold. -Nanoparticles into DMNs more mechanical strength 5.31 N, compared to only liraglutide DMNs 4.32 N. -Non-invasive, cost-effective, and user-friendly. -DMNs are showing fast release within minutes, but nanoparticles prepared DMNs show sustained release (48).
Sucrose/polyvinyl alcohol	Liraglutide	Dissolving microneedle	-Sufficient mechanical strength and no skin irritation. -Relative bioavailability of MNs was 69.8% and 46.3% compared to subcutaneous injection. -The presence of liraglutide at the microneedle (MN) tips was confirmed using Raman imaging -Dissolving MNs with pure drug-loaded tips were well tolerated with repeated once-daily dosing for 7 days at the same application site. -Higher drug loading capacity up to 2

			mg in a compact patch size of 0.9 cm^2 and successfully delivered up to 0.9 mg of liraglutide into porcine skin (49).
Starch/gelatin	Fluorescein isothiocyanate/ insulin	Dissolving microneedle	-Sufficient mechanical strength, *in vitro* ~200 µm and *in vivo* rat skin into 200–250 µm. -Administration using a applicator -Relative bioavaibility and relative pharmacological availability was observed approximately 92%. -Confirmed storage stability that over 90% of remained in the MNs after one month of storage at 25°C or 37°C (50).
Gelatin/sodium carboxymethyl cellulose	Fluorescein isothiocyanate/ insulin	Dissolving microneedle	-Optical coherence tomography was used to determine depth of MN penetration. -Confocal microscopy images revealed that rhodamine 6G gradually diffused from the puncture sites into the deeper layers of dermal tissue. -The relative bioavailability of microneedle compared to hypodermic injection was found to be satisfactory. -Tissue-marking dye was used to determine the *in vitro* skin insertion capabilities. -*in vivo* imaging system**,** skin regions treated with drug-loaded MNs exhibited strong fluorescence signals, which significantly diminished within 1 h post-application (51).

Sodium alginate/maltose	Insulin	Micromoulding	-Alginate cross-linked with maltose. -Good mechanical properties, excellent biocompatibility, excellent cytocompatibility. -More pharmacological activity, revealing a sustained lowering glucose levels with the relative bioavailability and relative pharmacological availability at 93.7 ± 4.7% and 94.1 ± 5.6%, compared with subcutaneous injection. -Showed excellent dissolution and swelling properties (52).
Xylitol/mannitol/resin/dental SG	Insulin	3D printed Steriolithography	-The optimized of MNs, are fabricated by using 3D printing technology, they reveled superior skin penetration capabilities and Compared to metal arrays, they required minimal force within the range of 2 to 5 N. -Micro-computed tomography analysis confirmed deep penetration and strong adhesion within the skin. -*In vivo* studies showed a rapid and effective glucose-lowering effect, achieving significantly reduced glucose levels within 60 min. -Combined with steady-state plasma glucose levels over a 4h, compared to subcutaneous injections (53).

3. Objectives of study

On review of the literature, it was found that microneedles made from natural polymers have a wide scope, significant potential, and growing interest in pharmaceutical formulations for drug delivery systems. Therefore, the objective of this study is:

1. To design and develop polymer-based microneedles systems for the transdermal delivery of antidiabetic agents.
2. To evaluate the fabricated microneedles through comprehensive *in vitro* and *in vivo* studies for their efficacy, biocompatibility, and therapeutic potential in the management of diabetes.

4. Plan of work

- Literature review
- Procurement of polymers and active pharmaceutical ingredients.
- Fabrication of drug-loaded polymeric microneedles using the micromoulding technique.
- Characterization of the fabricated microneedles using scanning electron microscopy studies, Fourier-transform infrared spectroscopy, and thermogravimetric analysis and mechanical strength and insertion properties.
- Evaluation of *in vitro* release and *ex vivo* permeation studies.
- Evaluation of biocompatibility of the microneedles
- *In vivo* evaluation of polymeric microneedles for diabetes treatment using animal models.
- Conduct comprehensive statistical analysis to interpret and evaluate the collected data.

5. Scope and Relevance

The extensive literature on this topic highlights that microneedles are becoming an increasingly important component of drug delivery applications. The field of biomaterials and biodegradable polymers has played a crucial role in developing advanced drug delivery systems. One notable technological advancement in transdermal drug delivery is the development of dissolving microneedles, which efficiently deliver therapeutics through the rapid dissolution of polymers after penetrating the skin. Microneedles offer several advantages, including: (a) large molecules can be administered, (b) it avoids first-pass metabolism, (c) it provides better and faster healing than the hypodermic needle at injection site, (d) pain free, easy administration, (e) avoids side effects like weight increase and hyperglycemia, (f) reduce the over dosage (54). Furthermore, the global microneedle market, valued at approximately USD 549.15 million in

2022, is projected to reach USD 979.39 million by 2030. Undoubtedly, significant research efforts will continue to drive the development of commercially viable, natural polymers based microneedle systems and technologies. The pursuit of new, efficient, and non-toxic drug delivery strategies remains a key focus for future advancements.

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